Potential Association of Posttraumatic Stress Disorder and Decreased Bone Mineral Density in Repatriated Prisoners of War

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ABSTRACT Objective: We conducted a retrospective evaluation of bone mineral density data collected during routine medical follow-up evaluations of 241 Vietnam-era male repatriated prisoners of war, with and without the lifetime diagnosis of posttraumatic stress disorder (PTSD), and 79 subjects in a comparison group. Methods: Dual-energy X-ray absorptiometry scans evaluated total hip and lumbar spine T-scores. A multivariate analysis of covariance was performed on the data using age, body mass index, ethnicity, and reported alcohol consumption as covariates. Results: There was a significant effect of group on total hip, but not lumbar spine, T-scores. Pairwise comparisons revealed statistically lower total hip T-scores in repatriates with a lifetime history of PTSD in comparison to both the comparison group and repatriates without a lifetime history of PTSD. Conclusion: In this study of elderly repatriated prisoners of war, we noted an association between a lifelong history of PTSD and decreased bone mineral density at the hip.

INTRODUCTION

Osteoporosis is defined as a systematic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone with an increase in bone fragility and susceptibility to fracture.[1] Male osteoporosis is a less well-recognized and studied condition compared to osteoporosis in women. It is known that approximately 1–2 million men in the United States have osteoporosis and another 8–13 million have osteopenia or decreased bone mass.[2] One-third of hip fractures occur in men, and more men than women die as a result of complications following the fracture.[3] Fractures tend to occur in men about 1 decade later than in women, presumably because they have larger bones and greater peak bone development.[4] Loss of bone mass in men, therefore, has significant medical and financial implications. The National Osteoporosis Foundation published the latest guidelines in 2010 for the prevention and treatment of osteoporosis in men and women. It is now recommended that men 70 years of age and older receive screening with dual-energy X-ray absorptiometry (DXA). Men younger than 70 years of age should also be screened if they have risk factors for bone loss.[5] In addition, in 2008, the World Health Organization developed a new calculator for the 10-year probability of a major osteoporotic fracture or specifically hip fracture based on hip DXA scores and multiple risk factors that now include gender and ethnicity.[6] It is likely that these new initiatives will result in more attention given to the issue of male bone mineral density (BMD) loss and more risk factors discovered.

Multiple risk factors for bone loss in men have been described and include the common factors of ethanol use, tobacco use, prior significant doses of glucocorticoids, low vitamin D levels, hypercalciuria, and hypogonadism.[7] Furthermore, 40% to 50% of cases are classified as idiopathic, that is, arising from unknown or obscure causes such as subclinical hypercortisolemia.[8] Other risk factors such as genetics[9] likely contribute to bone loss, and other factors are yet to be determined.

Captivity in a prisoner of war (POW) or concentration camp is associated with multiple risk factors for bone loss such as dietary deficiencies in protein, vitamin D, and calcium; immobility; and lack of sunlight. Several studies have confirmed the increased incidence of fragility fractures as well as radiographic evidence of bone loss in World War II and Vietnam era POW.[10–13] Evidence to date, however limited, suggests repatriation is associated with reversal of weight loss and reversal of bone loss in a majority of patients.[14] Therefore, captivity may explain short-term bone loss, but not chronic loss, decades later. Other risk factors must be evaluated if bone loss persists in repatriated prisoners of war (RPWs).

Depression has been associated with decreased BMD in both men and women in multiple studies.[15–17] In a study of women with a current or past history of depression, they were found to have decreased BMD at all trabecular bone areas, except the wrist that is largely cortical bone, compared to normal controls. Urinary cortisol levels were higher and osteocalcin (a marker for osteoblastic activity) was lower than noted in controls. Urinary deoxypyridinoline (a marker for bone resorption) levels were also lower than controls, suggesting decreased bone turnover.[18] Most studies of depressed individuals have shown urinary cortisol levels higher than controls but not elevated above the normal range. It is thought that mild relative hypercortisolism is the mechanism for decreased BMD associated with depression. This is further substantiated by trials, which have shown that excess endogenous or exogenous glucocorticoids decrease bone formation and are associated with primarily trabecular bone loss.[19–21] Depression,

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14. ABSTRACT

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15. SUBJECT TERMS

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therefore, is a risk factor for decreased BMD likely because of chronic changes in the neuroendocrine system.

Acute stress, chronic stress, and posttraumatic stress disorder (PTSD) are associated with multiple abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis, gonadal–pituitary axis, and the autonomic nervous system.[22] In a study by Morgan,[23] military subjects undergoing acute stress in survival training showed significant elevations of serum cortisol and thyroid stimulating hormone but reductions in testosterone, total and free T4, and total and free T3. It is possible that prolonged severe stress, like that experienced in a POW camp, could affect neuroendocrine stress markers, leading to bone loss. Prior studies of combat-related PTSD in Vietnam-era subjects, years after combat, have shown conflicting results in terms of serum and urinary cortisol excretion.[24–26] Furthermore, 2 studies have demonstrated elevated basal levels of corticotropin-releasing hormone in subjects with combat-related PTSD.[27,28] Yehuda[29] and others have hypothesized that there is an enhanced negative feedback inhibition of cortisol on the HPA axis in PTSD patients, but the process is complex and dynamic. Chrousos points out that stress also activates the release of inflammatory cytokines such as interleukin-6, which stimulate the HPA axis, resulting in higher levels of cortisol and stimulation of osteoclasts, potentially leading to bone resorption.[30,31]

Thus, earlier studies suggest a link between BMD loss and prolonged psychological stress and/or depression. These findings prompted us to evaluate our data collected on a unique cohort of military combat Vietnam-era veterans, many of whom are former POW.

Several retrospective pilot analyses have been conducted with BMD data collected from male patrons who regularly visit the Robert E. Mitchell Center for Prisoner of War Studies located in Pensacola, Florida. This voluntary medical and psychological evaluation program has been available to Vietnam War-era RPWs since 1973. A matched comparison group (CG) of combat experienced male aviators who were not held prisoner by the Vietnamese but were otherwise similar to the Vietnam-era repatriates (e.g. age, education, aircraft flown, combat flight hours, marital status, and rank) have also been patrons of the Center since 1976.

In 1999, the Robert E. Mitchell Center noted that BMD (measured by computed tomography of the lumbar spine) was lower in RPWs compared to a CG of age-matched male aviators. A 2001 retrospective pilot analysis of hip BMD data by DXA suggested RPWs with PTSD were twice as likely to have osteopenia compared to RPWs without PTSD and the CG.[32] As this database grew with more subjects screened with the DXA scan, it was decided to conduct the current retrospective study of the now larger data set to determine if there was a relationship between PTSD and BMD loss. Age, body mass index (BMI), alcohol use, and ethnicity were covariates in our analyses. In addition, we determined if bone loss correlated with years in captivity, weight loss during captivity, duration of solitary confinement, or severity of torture. We anticipated that evaluation of total hip T-scores would be more accurate than total spine T-scores because of the increased incidence of lumbar spine osteoarthritis in elderly men that falsely raises the T-score.[33] The T-score measures the SD between a participant's BMD score and that of a young–adult reference population mean. A T-score that is 2.5 SDs or more below the young–adult reference population is defined as osteoporosis; 1–2.5 SDs below the young–adult reference population is defined as osteopenia. Z-scores compare the patient's BMD to an age-matched population. A Z-score of −2.0 or lower is considered below the expected range for age.[34]

METHODS

Participants

The Robert E. Mitchell Center for Prisoner of War Studies is a unique institution that holds the only longitudinal study of the long-term effects of the POW experience currently in existence. Many of the participants have been routinely medically and psychologically evaluated since 1973 to present date (2010). There are 557 participants in the center's database, with 439 RPWs and 118 CG participants matched by age, education, gender, and combat experience. Repatriates from all services and all recent U.S. conflicts (1959–1975 Vietnam, 1990–1991 Gulf War, 1992–1993 Somalia, 1992–1995 Bosnia, and 2003 Iraq) are in this program, but only the data from the Vietnam-era participants were included in this retrospective analysis.

Although data was gathered as part of a routine medical evaluation, participants signed informed consent forms enabling the Center to analyze data for research purposes. The research proposal was approved by the Naval Medical Center Portsmouth Institutional Review Board.

Measures

DXA exams for this cross-sectional study were selected from the initial studies performed in the 2006–2007 time frame. The DXA scan BMD data from 320 participants was subsequently divided into 3 groups: the CG consisting of 79 combat-experienced non-RPWs without PTSD (CG PTSD−); a group of 180 RPWs without a lifetime history of PTSD (RPW PTSD−); and a group of 61 RPWs with a lifetime diagnosis of PTSD (RPW PTSD+). The diagnosis of PTSD was made clinically using Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria in the 1997–1998 time frame.[35] Participants with a lifetime diagnosis of depression were excluded because of the known association of depression and bone loss. A total of 20 participants were excluded because of a lifetime diagnosis of depression; 10 had major depression alone and 10 had major depression and PTSD. The study also excluded individuals who had lumbar spine osteoarthritis with BMD values greater than 3 SDs above the norm.

The psychological evaluations of these participants included record review and clinical interview and administration of the following psychometric instruments: the Geriatric Depression

Scale (GDS), the Peritraumatic Dissociation Experience Questionnaire (PDEQ), and the revised Impact of Events Scale (IES-R). The GDS was developed specifically as a screening instrument for use with older patients, and it excludes the nonspecific physical symptoms of depression found in similar instruments used with younger patients.[36] Scores above 9 on the 30-item GDS are suggestive of Mood Disorder (major depression or bipolar disorder) in the general population, although the suggested cut-off for military aviators is a score of 5.[37]

The PDEQ is a 10-item, Likert-type scale with demonstrated utility in predicting PTSD in the general population.[38] Among military aviator repatriates, PDEQ score is highly predictive of PTSD symptoms and diagnosis and as solitary confinement.[39,40] Although not designed for PTSD diagnosis,[41] the 22-item IES-R is useful for monitoring the presence and severity of PTSD symptoms. As the DSM-IV requires 1 intrusive symptom, 3 avoidance symptoms, and 2 hyperarousal symptoms, the pattern of IES-R may be evaluated as a screen for PTSD diagnosis, along with IES-R total score.[42]

Data Analyses

The Statistical Package for the Social Sciences (SPSS, Chicago, Illinois) was used for the analysis. A multivariate analysis of covariance (MANCOVA) was performed on the primary dependent variables of interest associated with BMD: total hip T-score and total lumbar T-score. Adjustment was made for 4 covariates: age, BMI, ethnicity, and reported alcohol consumption. The independent variable was group (CG, repatriates without a lifetime history of PTSD, and repatriates with a lifetime history of PTSD). Tobacco use was analyzed among the 3 groups and not found to be statistically different [$F(2,313) = 6.27$, $p = 0.18$] and therefore not used as a covariate (Table I). Although there was no missing data, the total number of participants' data ($N = 322$) were reduced to 320 because of the presence of 1 univariate (BMI) and 1 multivariate outlier (BMI × age), using $\alpha = 0.001$.[43] The results of an evaluation of the assumptions of normality, homogeneity of variance–covariance matrices, linearity, and multicollinearity were satisfactory. In addition, the covariates were judged to be reliable for this MANCOVA. This analysis used a Type III sum of squares (unweighted means) in view of the unequal number of subjects in each group.

RESULTS

As shown in Table I, with the exception of the reported alcohol use, $F(2,313) = 16.51$, $p < 0.01$, the groups were equivalent with regards to age, $F(2,313) = 0.70$, $p = 0.48$; BMI, $F(2,313) = 1.8$, $p = 0.17$; and ethnicity, $F(2,313) = 2.28$, $p = 0.32$. Table I presents the data for alcohol use and smoking history frequency counts across groups.

The estimated loss of weight in captivity, $t(239) = 0.06$, $p = 0.81$, length of captivity, $t(239) = 0.04$, $p = 0.97$, severity of torture, $t(239) = 0.1.29$, $p = 0.20$, and solitary confinement, $t(239) = 0.1.73$, $p = 0.88$, were not statistically different between the 2 groups (Table II). The similarities between the 2 RPW groups with respect to captivity duration, solitary confinement duration, estimated weight loss, and subjective rated torture severity are reported in Table II.

The group-level descriptive statistics for the psychometric instruments can be found in Table III. Analysis of psychological testing revealed that depressive symptoms were more common in the RPW PTSD+ group than in the RPW PTSD− group or the CG PTSD− group, even after participants with prior clinical depression were excluded [$F(2,313) = 7.89$, $p < 0.001$]. Although subjects were excluded on the basis of a lifetime diagnosis of mood disorder, RPW PTSD+ subjects (mean = 4.8, SD = 4.7) reported more depressive symptoms than did members of the CG PTSD− (mean = 2.8, SD = 3.0) and the RPW PTSD− (mean = 2.8, SD = 2.8) group. However, mean scores are within normal limits for the GDS.

TABLE I. Group Level Comparisons of Age, BMI, Alcohol Use, Smoking, and Ethnicity

	CG PTSD− ($N = 79$)	RPW PTSD− ($N = 180$)	RPW PTSD+ ($N = 61$)	F	p
Age[a]	63.4 (5.4)	62.9 (5.9)	62.2 (6.1)	0.7	0.48
BMI[a]	26.7 (3.3)	27.3 (3.4)	27.8 (3.4)	1.8	0.17
Reported Alcohol Use[b]					
Abstain	19 (24)	19 (11)	6 (10)		
Light	33 (42)	67 (37)	30 (49)		
Moderate	19 (24)	79 (44)	19 (31)		
Heavy	8 (10)	15 (8)	6 (10)	16.51[c]	0.01
Reported Smoking History[b]					
Nonsmoker	32 (41)	55 (31)	18 (30)		
Former Smoker	44 (56)	120 (67)	38 (62)		
Current Smoker	3 (4)	5 (3)	5 (8)	6.27[c]	0.18
Year (Quit)	1980	1980	1982	0.48	0.62
Pack-Years (Mean)	17	16	21	1.00	0.37
Ethnicity[b]					
Caucasian	78 (99)	177 (98)	59 (97)		
African American	1 (1)	3 (2)	2 (3)	2.28[c]	0.32

[a]Mean (SD). [b]Number (Percent). [c]Chi-square statistic.

Other tests such as the PDEQ and IES-R also showed a statistically significant difference between the RPW PTSD+ group compared to the other 2 groups. There were significant differences between the groups in the number of retrospectively reported dissociative symptoms [$F(2,313) = 41.79$, $p < 0.001$], with RPW PTSD+ subjects (mean = 19.3, SD = 8.5) reporting the greatest number of symptoms and CG PTSD– subjects (mean = 11.5, SD = 2.5) reporting the fewest number of symptoms. As would be predicted on the basis of the presence or absence of a clinical PTSD diagnosis, RPW PTSD+ subjects differed from the other 2 groups on the IES-R with respect to both the total number of symptoms [$F(2,313) = 70$, $p < 0.001$] and their reported total rated severity [$F(2,313) = 54.77$, $p < 0.001$]. Group differences were also noted on IES-R symptom measures of intrusions, $F(2,313) = 48.14$, $p < 0.001$; avoidance, $F(2,313) = 37.48$, $p < 0.001$; and arousal, $F(2,313) = 86.84$, $p < 0.001$ (Table III). These results not only support the clinical diagnosis of PTSD in the RPW PTSD+ group, they also highlight the similarities between the 2 non-PTSD groups with respect to depression and PTSD at the symptom level.

MANCOVA results revealed significant differences among group category on the combined dependent variable, using Roy's Largest Root = 0.05, $F(2,313) = 3.02$, $p < 0.05$, multivariate $\eta^2 = 0.02$. The covariate age significantly influenced the combined dependent variable, Roy's Largest Root = 0.08, $F(2,312) = 12.90$, $p < 0.0001$, multivariate $\eta^2 = 0.08$. The covariate BMI significantly influenced the combined dependent variable, Roy's Largest Root = 0.11, $F(2,312) = 16.53$, $p < 0.0001$, multivariate $\eta^2 = 0.10$. The covariate of alcohol use, however, did not significantly influence the combined dependent variable, Roy's Largest Root = 0.001, $F(2,312) = 0.20$, $p < 0.82$, multivariate $\eta^2 = 0.001$. The covariate ethnicity did not significantly influence the combined dependent variable, Roy's Largest Root = 0.006, $F(2,312) = 0.93$, $p < 0.40$, multivariate $\eta^2 = 0.006$.

Analysis of covariance was conducted on each dependent variable as a follow-up test to MANCOVA. Group differences were significant for total hip T-scores [$F(2,313) = 3.02$, $p < 0.05$, partial $\eta^2 = 0.02$] but not for total spine T-scores [$F(2,313) = 1.54$, $p < 0.22$, partial $\eta^2 = 0.01$] after controlling for age, BMI, ethnicity, and alcohol use. The estimated marginal mean total hip T-scores for each group were as follows: CG PTSD– = –0.079 (95% confidence interval [CI] = –0.266 to 0.109); RPWs PTSD– = –0.076 (95% CI = –0.199 to 0.047); and RPWs PTSD+ = –0.371 (95% CI = –0.583 to –0.160; Fig. 1). Pairwise comparisons based on these estimated marginal means revealed statistically lower total hip T-scores in the RPW PTSD+ group, in comparison to both the CG (mean difference = –0.29, $p = 0.04$) and the RPW PTSD– group (mean difference = –0.30, $p = 0.02$), although the mean difference between the CG PTSD– group and the RPW PTSD– group was not significant.

TABLE II. Group Level Comparisons of Captivity Duration, Solitary Confinement Duration, Torture Severity, and Estimated Weight Loss

	RPW PTSD–	RPW PTSD+	*t*	*p*
Captivity Duration (Months)	53.2 (31.2)	53.0 (30.6)	0.04	0.97
Solitary Confinement (Weeks)	27.9 (41.2)	43.6 (66.9)	1.73	0.09
Rated Torture Severity (0–75)	29.2 (10.3)	31.2 (11.7)	1.29	0.20
Estimated Weight Loss (Lbs)	43.6 (25.6)	44.5 (25.0)	0.06	0.81

DISCUSSION

This retrospective study of DXA scan BMD data demonstrated that the lifetime diagnosis of PTSD in our Vietnam-era RPW population was associated with decreased BMD, as manifested by a lower total hip T-score, compared to RPWs without PTSD and the CG. The results indicate that PTSD may be a risk factor for bone loss in this group of elderly men. To our knowledge, this is the first study to report an association between lifetime diagnosis of PTSD and BMD loss by DXA.

In this study, the RPW PTSD–, CG PTSD–, and RPW PTSD+ groups had BMD Z-scores, respectively, of 0.43, 0.42, and 0.18 SDs higher than the age-matched population at large. This suggests that a history of remote captivity alone does not predict or explain future bone loss. Our results are in agreement

TABLE III. Group Level Comparisons of Psychometric Tests

	CG PTSD– (*N* = 79)	RPW PTSD– (*N* = 176)	RPW PTSD+ (*N* = 61)	*F*	*p*	Group Comparisons[a,b]
GDS Total	2.8 (3.0)[c]	2.8 (2.8)	4.8 (4.7)	7.89	<0.001	1,2<3
PDEQ Total	11.5 (2.5)	14.6 (4.2)	19.3 (8.5)	41.79	<0.001	1<2<3
IES-R						
Total No. of Symptoms	1.8 (3.0)	3.0 (3.6)	9.7 (6.8)	70.00	<0.001	1,2<3
No. of Intrusion Symptoms	1.1 (1.7)	1.7 (1.9)	4.3 (2.8)	48.14	<0.001	1,2<3
No. of Avoidance Symptoms	0.6 (1.3)	1.0 (1.5)	3.0 (2.7)	37.48	<0.001	1,2<3
No. Arousal Symptoms	0.1 (0.4)	0.4 (0.9)	2.5 (2.1)	86.84	<0.001	1,2<3
Total Rated Severity	2.5 (5.1)	3.9 (5.0)	15.7 (13.4)	54.77	<0.001	1,2<3
Rated Intrusion Severity	1.5 (2.8)	2.2 (2.8)	6.8 (5.5)	49.63	<0.001	1,2<3
Rated Avoidance Severity	0.9 (2.5)	1.2 (1.9)	4.9 (5.4)	39.07	<0.001	1,2<3
Rated Arousal Severity	0.2 (0.6)	0.5 (1.3)	1.9 (4.1)	69.28	<0.001	1,2<3

[a]Scheffe. [b]1, CG PTSD–; 2, RPW PTSD–; 3, RPW PTSD+. [c]Mean (SD).

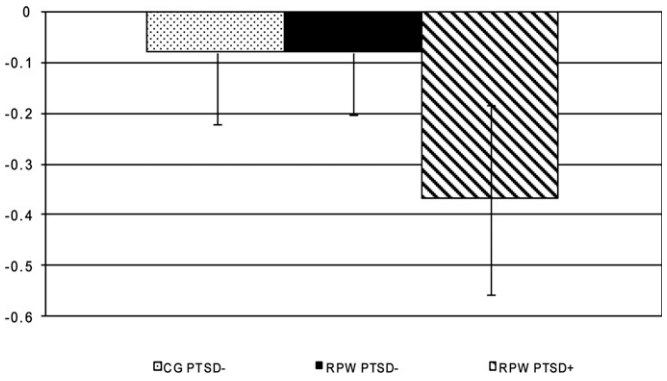

FIGURE 1. Estimated marginal means total hip T-scores (columns) with 95% CI (bars).

with studies demonstrating bone loss based on standard radiography that occurs during captivity, which later improves with increased nutrition and weight gain.[13] Similarly, a study of elderly women who were survivors of the Holocaust and aged 17 and older in 1945 failed to show a higher incidence of osteoporosis by DXA, compared to controls. However, Holocaust survivors younger than 17 years of age in 1945 had a higher incidence of osteoporosis vs. controls, presumably because of decreased peak bone mass. This study did not comment on the presence or absence of PTSD in the survivors.[44] We are unaware of any similar DXA study in male Holocaust survivors.

The observed association between the RPW PTSD+ group and decreased BMD is not explained by the common risk factors of age, BMI, alcohol use, tobacco use, and ethnicity. Furthermore, the estimated loss of weight in captivity, length of captivity, severity of torture, and solitary confinement duration were not statistically different between the 2 groups. Because depressive symptoms on the GDS were more common in the RPW PTSD+ group than in the RPW PTSD− group or the CG PTSD− group, we also evaluated the 20 excluded subjects with major depression and noted no significant difference in age, ethnicity, BMI, or alcohol use. The mean BMD of the 20 excluded subjects was −0.0285 (0.778), nearly identical to the RPW PTSD− and CG means. Therefore, we do believe that the minimal depressive symptoms observed on the GDS in the RPW PTSD+ group explain their BMD loss.

Although we corrected our analysis for the standard risk factors for bone loss, other covariates may exist. The hypothesis that RPWs with PTSD have bone loss associated with alterations in neuroendocrine stress system will require further extensive testing. To evaluate the relationship between PTSD and bone loss further, we propose to expand medical histories to include history of fragility fractures, average calcium intake, exercise, vitamin D intake, and the use of thiazides, steroids, and anticonvulsants. We will need to evaluate the HPA and gonadal axes and the standard blood and urine tests to evaluate secondary causes of bone loss, including markers of bone formation and bone resorption.

Our study has several limitations. The effect size of the association between BMD loss and PTSD is small (i.e., η^2 = 0.02), and although it is statistically significant, it is not clinically significant. Also, a statistically significant association does not prove cause and effect. We should also state that we cannot generalize the findings in this study to other populations, such as younger subjects, female subjects, those with more recent PTSD or PTSD that is non–combat related or not related to prior captivity as a POW. Although our participant population of elderly well-educated male aviators does not reflect the population at large, a strength of this study is that it allowed an analysis of BMD with fewer confounding comorbidities.

In conclusion, our study demonstrated that DXA total hip T-scores were statistically significantly lower in the RPW PTSD+ group compared to the RPW PTSD− group or the CG PTSD− group. This suggests that a lifetime diagnosis of PTSD may be associated with loss of BMD through mechanisms yet to be determined. Further studies are necessary to evaluate this relationship.

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